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Coagulation dysfunction of severe burn patients: A potential cause of death

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ABSTRACT

Background: Research on coagulation dysfunction following burns is controversial. This study aimed to describe the coagulation changes in severe burn patients by examining coagulation parameters.

Methods: Patients with third-degree total body surface area (TBSA) burns of ≥30% were enrolled between 2017 and 2020. Platelet (PLT) count and coagulation indexes (including APTT, INR, FIB, DD, and AT III) were measured at admission and once weekly for 8 weeks, and statistical analysis was performed. The patient medical profiles were reviewed to extract demographic and clinical data, including TBSA, third-degree TBSA, and inhalation injury. The total intravenous fluids and transfusions of crystalloids, fresh frozen plasma (FFP), and red blood cells (RBC) were calculated during the forty-eight-hour period. The number of sepsis cases was recorded.

Results: We enrolled 104 patients , and while the overall coagulation trend fluctuated, inflection points appeared around one week and demonstrated hypercoagulability. INR was significantly higher in the non-survival group than in the survivors' group from admission to three weeks after burn (all $p < 0.01$). From post-injury week 1 to post-injury week 3, the APTT in the non-survival group was greater than in the survival group, but the non-survival group's PLT count was lower than that in the survival group (all $p < 0.05$). At two and three weeks after burns, the FIB levels in the non-survival group were significantly lower than those of the survival group (both $p < 0.01$). The prevalence of inhalation injury and the proportion of sepsis cases were significantly higher in the non-survival group than in the survival group ($p < 0.05$, $p < 0.001$, respectively). At the time of death, APTT, INR, and FDP levels were significantly higher in the non-survival group in the survivor group, and FIB, ATIII, and PLT were significantly lower than in the survivor group (all $p < 0.01$). On the day of death, nine of the 12 dead patients had disseminated intravascular coagulation (DIC).

Conclusions: Coagulation dysfunction was most prominent in severe burn patients 1 week after injury and presented as hypercoagulability. Large-area burn injury, large amounts of

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fluid resuscitation, inhalation injury, and sepsis may all contribute to coagulation dysfunction, which can further develop into DIC and even death in severe burns patients.
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1. Introduction

At the moment, consensus exists that severe tissue damage and systemic hypoperfusion as a result of bleeding are the primary causes of acute traumatic coagulopathy (ATC) [1-3]. Severe burns are a form of very fatal trauma and one of the leading causes of mortality and disability worldwide, and patients with thermal injury exhibit a comparable coagulation abnormality. However, coagulation dysfunction associated with burns is not identical to ATC [1,3-6]; in comparison to patients with severe trauma, patients with severe burns consume a large number of coagulation factors and other regulatory proteins following injury. Although it has been demonstrated that severe burns result in an imbalance of the coagulation, fibrinolytic, and inflammatory systems [6], the precise underlying mechanism of coagulation dysfunction remains unknown.

Inhalation injury and sepsis occur at a relatively high rate in severe burn patients and have a detrimental effect on their prognosis [7-9]. Apart from respiratory failure and septic shock, inhalation injury can result in coagulation disorders in the lungs, and sepsis can readily cause disseminated intravascular coagulation (DIC) [8-10], which might impair coagulation in patients with severe burns. Currently, there is a dearth of research on coagulation function following severe burns. Therefore, the purpose of this study was to describe the coagulation function of severe burn patients and investigate the potential causes of their occurrence by analysis of coagulation parameters and other clinical data.

2. Methods

2.1. Study design and participants

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Inner Mongolia Medical University. All patients signed an informed consent, which was followed by the collection of patient information and blood.

Using the institution's Burn Registry, all burn patients admitted in burn intensive care units (BICU) between March 2017 and December 2020 were evaluated, who 1) were 18 years of age or older, but under 65, 2) had a third-degree total body surface area (TBSA) ≥30%, and 3) were admitted less than 12 hours after injury. Patients were excluded if they 1) had coagulation dysfunction, including congenital or primary liver damage or long-term alcoholism, 2) had taken anticoagulant drugs within six months of injury, including heparin, a vitamin K antagonist, or had taken aspirin for a long time, or 3) had received antithrombin or activated protein C treatment.

2.2. Treatments

Patients' conditions were further treated based on disease progression. Patients were first admitted to the hospital to establish intravenous access to receive a combination of crystalloid fluid and fresh frozen plasma (FFP) for anticonvulsant therapy. The patients' rehydration rate and volume were regulated appropriately based on the use of an indwelling catheter to monitor the hourly urine volume and the color of the urine. Inhalation injury was diagnosed based on the patient's history of exposure to smoke in a closed space and the bronchoscopy findings, and tracheotomy was performed in the event of respiratory distress or airway obstruction. Escharotomy was used to decompress areas at risk of developing compartment syndrome; if decompression was unsuccessful and the intrafascial pressure exceeded 30 mmHg (measurement tool: Stryker intracavitary pressure monitor). Fasciotomies were performed to further reduce the pressure. Surgeries such as debridement, resection, and grafting were performed as soon as the patients' vital signs stabilized, and some patients received red blood cells (RBC) therapy based on their bleeding volume. Appropriate antibiotics were selected based on wound culture or blood culture results, as well as antibiotic profiles.

2.3. Data sources

The patients were divided into a survival group and a non-survival group based on the prognosis. Patients' demographic and clinical data, including age, sex, TBSA, third-degree TBSA, inhalation injury, number of operations (e.g., tracheostomy, escharotomy, fasciotomy, debridement, excision, and grafting), and central venous catheterization, total days in BICU, 48-h and total intravenous fluids and transfusion of crystalloids, 48-h and total intravenous fluids and transfusion of FFP, 48-h and total intravenous fluids and transfusion of RBC, and sepsis were collected. Venous blood samples were also collected on admission and weekly for at least 8 weeks to measure platelets (PLT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen (FIB), D-dimer (DD), and antithrombin III (AT III). Venous blood samples were also collected on the day of death from the dead patients. The kit instructions were referred to for information on normal ranges of APTT, INR, FIB, FDP, DD, ATIII, and PLT (all from Sysmex Corporation, Kobe, Japan).

The abbreviated burn severity index (ABSI) score, associated injuries, wound and blood culture results, as well as the presence of sepsis and DIC scores in all dead patients, were recorded. Sepsis was diagnosed using Sepsis-3 definitions [11], and DIC scores were calculated using the International Society on Thrombosis and Hemostasis (ISTH) [12].

2.4. Statistical methods

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 26.0, Chicago, USA). Graphing was performed using GraphPad Prism software (GraphPad Software, version 8.0, San Diego, CA). Data were expressed as mean ± standard deviation or medians and interquartile range (IQR: first quartile–third quartile) or frequency (n) and proportions (%). Multiple imputations (MI) or mean substitution were used to manage missing data, depending on the percentage of data missing. The data were analyzed using Analysis of Variance (ANOVA), independent

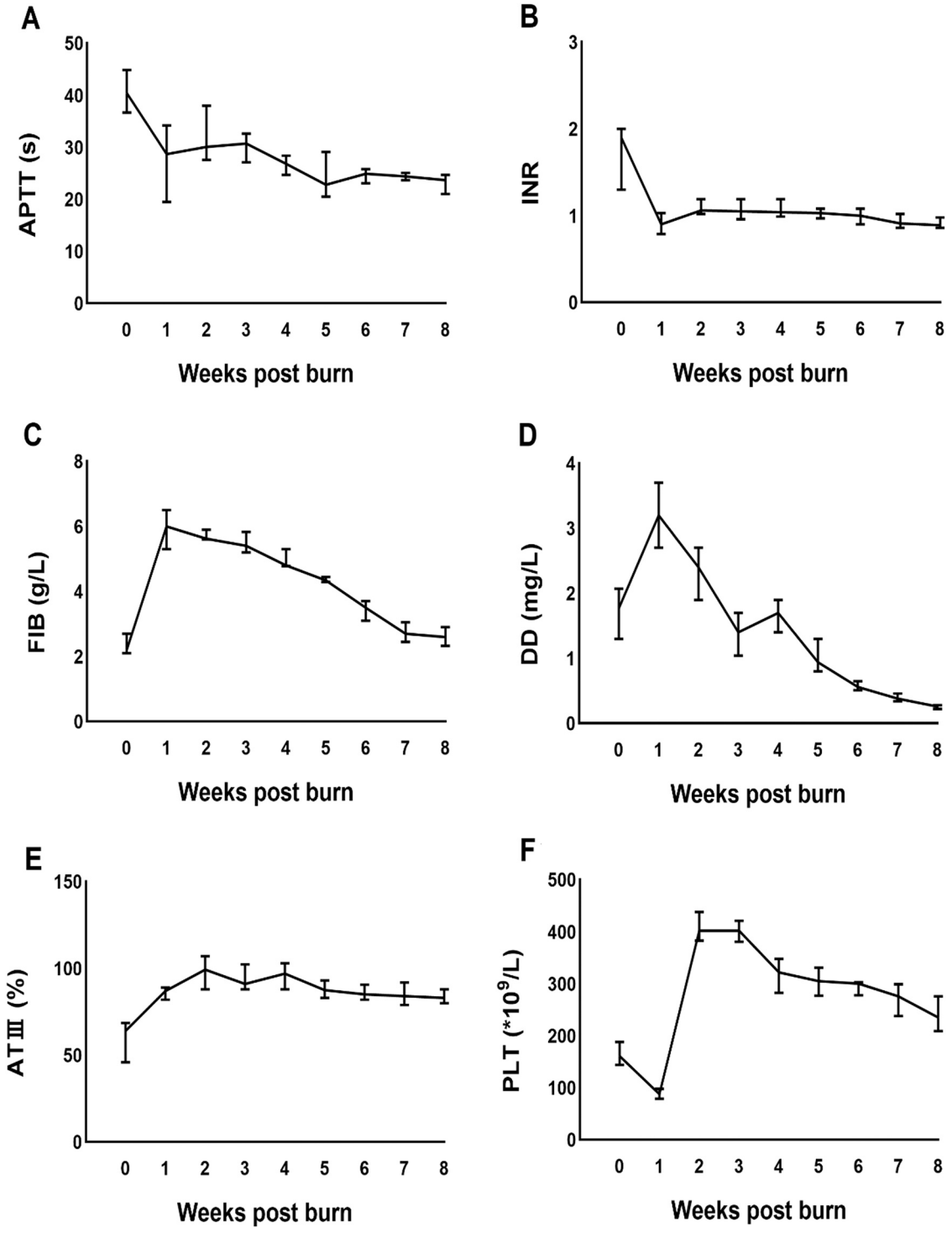

Fig. 1 – The curves of APPT (A), INR (B), FIB (C), DD (D), ATIII (E) and PLT (F) with time for all patients. The continuous lines represent the medians, while the whiskers represent the upper and lower quartiles. 0 on the x-axis denotes hospitalization.

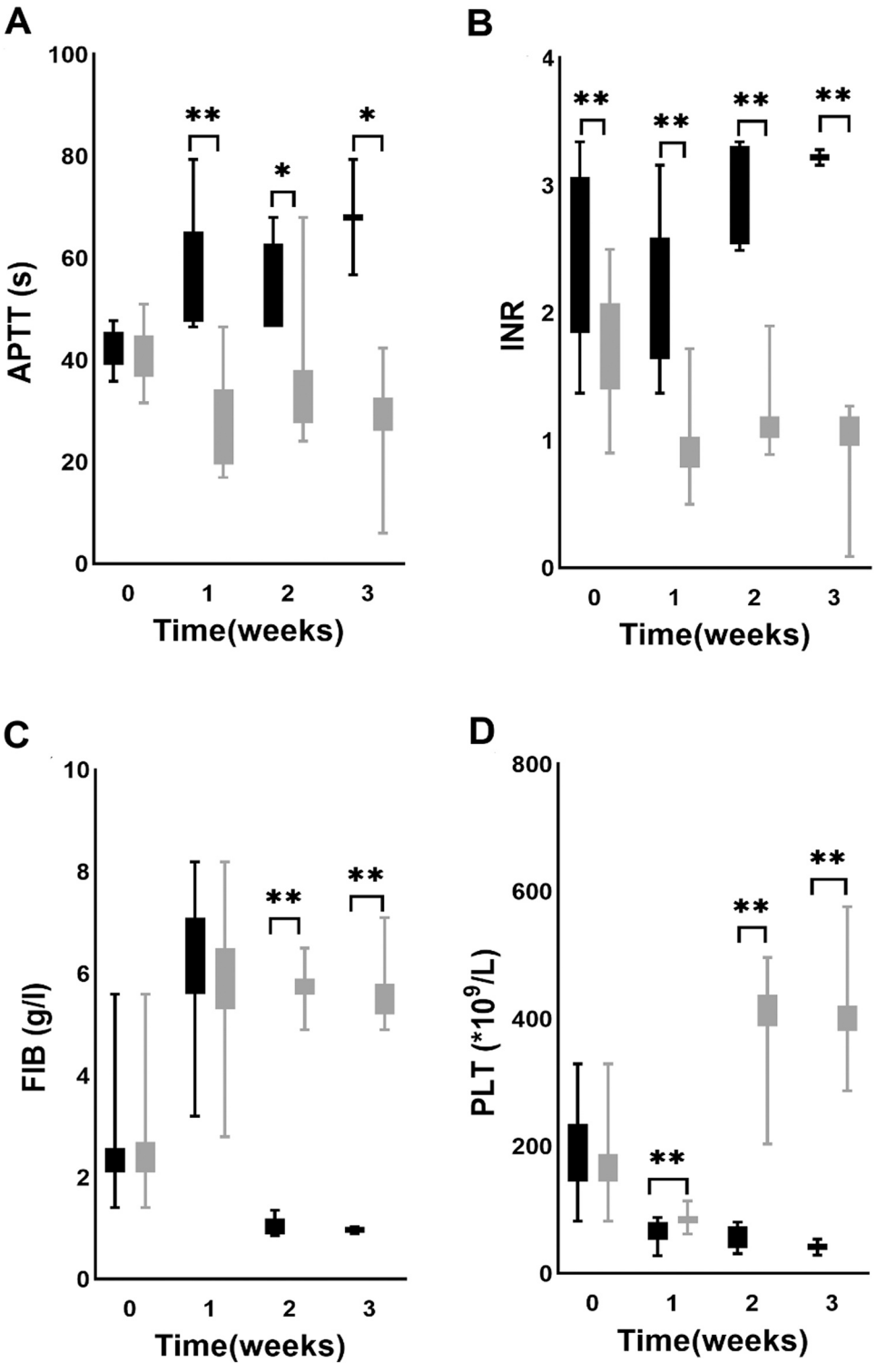

Fig. 2 – The boxplots of APPT (A), INR (B), FIB (C), and PLT (D) values for the non-survival and survival groups at admission and three weeks post-burn. The black boxes represent non-survival. White boxes represent the survival group. The boxes represent the upper and lower quartiles and the median, while the ends of the whiskers indicate the maximum and minimum values. 0 on the x-axis denotes hospitalization. The differences between the survival and non-survival groups were analyzed using repeated-measures ANOVA, and *, $p < 0.05$, **, $p < 0.01$.

sample t-test, the chi-squared test, and the Mann-Whitney U test. P values < 0.05 were considered statistically significant.

3. Results

A total of 104 patients were included in this study, 12 of whom died. Two patients in the survival group suffered coagulation complications, both with lower leg deep vein thrombosis; one patient developed this at 33 days after the burns and the other at 42 days, and both were successfully treated with anticoagulant therapy.

Coagulation indexes of all patients are shown as line graphs in Fig. 1. At admission, the median INR was significantly higher in the dead patients than in survivors (3.07 vs 1.9, $p < 0.01$, repeated-measures ANOVA, Fig. 2B). After 1 week of burns, in addition to having higher INR values than survivors, the non-survival group had higher APTT values than survivors (median: 51.85 s vs 28 s, $p < 0.01$, Fig. 2A), and PLT counts were lower in the non-survival group than survivors (median: 60 vs 87 * 10^9 /L, $p < 0.01$, Fig. 2D). Two weeks after burns, INR, APTT, and PLT counts were significantly different between the two groups (all $p < 0.05$), and FIB levels were significantly lower in the non-survival group than in the survival group (median: 0.95 vs. 5.62 mg/L, $p < 0.01$, Fig. 2C). INR, APTT, PLT, and FIB remained statistically different between the two groups three weeks after burns (all $p < 0.01$, Fig. 2).

The prevalence of inhalation injury was significantly higher in the non-survival group (58.3%) than in the survival group (23.9%) ($p = 0.012$, chi-square test, Table 1). The non-survival group had a significantly higher proportion of sepsis than the survival group (66.7% vs 15.2%, $p < 0.001$, chi-square test, Table 1). The number of patients transfused in the non-survival group was significantly higher than the survival group (83.3% vs 40.0%, $p < 0.05$, chi-square test, Table 1). Patients received significantly more total intravenous fluids and transfusions of FFP and RBC for forty-eight hours than the survival group (both $p < 0.05$, t-test, Fig. 3).

Comparing coagulation parameters between the dead patients on the day of death and survivors 4 weeks post-burns revealed statistically significant differences in all coagulation parameters except for DD volume (all $p < 0.01$, Mann-Whitney U tests, Fig. 4). APTT, INR, and FDP levels were significantly higher in the non-survival group than in the survival group, while FIB, ATIII, and PLT levels were significantly lower in the survival group.There were two female and ten male patients among the 12 non-survival patients. Five sustained additional injuries, including tension pneumothorax, multiple fractures, blast injury, and craniocerebral injury. Eight patients had a positive wound culture and seven patients had a positive blood culture, eight patients developed sepsis during the treatment period. On the day of death, nine patients were diagnosed with DIC (Table 2).

4. Discussion

Coagulation dysfunction is a leading cause of death during the first aid process in trauma patients [1-3]. Currently, only a few studies have delineated numerous distinctions between coagulation dysfunction associated with burns and ATC [1,3-6]. ATC occurs at the early stages of injury, before hospitalization, whereas the timing and molecular mechanisms of coagulation dysfunction following burns remain unknown [1,3,5]. In clinical practice, the issue of whether burn patients have coagulation dysfunction remains controversial [13-15]. Lu and King et al [5,13] found no evidence of postburn coagulopathy in burn patients with TBSA values ranging from 15% to 30%; nevertheless, other studies [2,4,16,17] have demonstrated that severe burns can result in systemic coagulation dysfunction. In this study, it was discovered that severe burns can result in coagulation dysfunction, which was significantly manifested as hypercoagulability one week

Table 1 – Comparisons of clinical outcomes between the survival and non-survival groups.

	Survival group (n = 92)	Non-survival group (n = 12)	*p*-value
Age	39.30 ± 12.90	44.19 ± 18.41	0.101
Sex ratio (F/M)	7/85	2/10	0.277
TBSA (%)	55.43 ± 13.76	66.92 ± 20.76	0.007
TBSA third degree (%)	33.23 ± 7.95	50.00 ± 16.37	0.000
Inhalation injury (n/%)	22/23.9	7/58.3	0.012
Number of operations*	3.59 ± 0.99	2.25 ± 0.62	0.000
Number of central venous catheterization	2.88 ± 1.63	2.67 ± 1.67	0.703
Total days in BICU	14.30 ± 4.77	11.42 ± 9.04	0.013
48-h crystalloids transfusion (ml)	7429.72 ± 1120.92	9483.33 ± 2270.58	0.005
48-h FFP transfusion (ml)	3535.17 ± 1085.60	4689.83 ± 1147.77	0.002
48-h RBC transfusion (U)	1.94 ± 1.03	2.88 ± 1.93	0.018
Total crystalloids transfusion (ml)	17463.61 ± 6439.33	24166.67 ± 9515.77	0.002
Total FFP transfusion (ml)	7123.61 ± 1955.98	11863.83 ± 6291.23	0.000
Total RBC transfusions (U)	11.00 ± 4.69	14.67 ± 5.93	0.009
Number of patients transfused (n/%)	34/40.0	10/83.3	0.002
Sepsis (n/%)	14/15.2	8/66.7	0.000

Abbreviations: F, female; M, male; TBSA, total burned surface area; BICU, burn intensive care unit; FFP, fresh frozen plasma; RBC, red blood cells; *including, tracheostomy, fasciotomies, debridement, excision, and grafting. Data are expressed as mean ± standard deviation or frequency (n) and proportions (%).

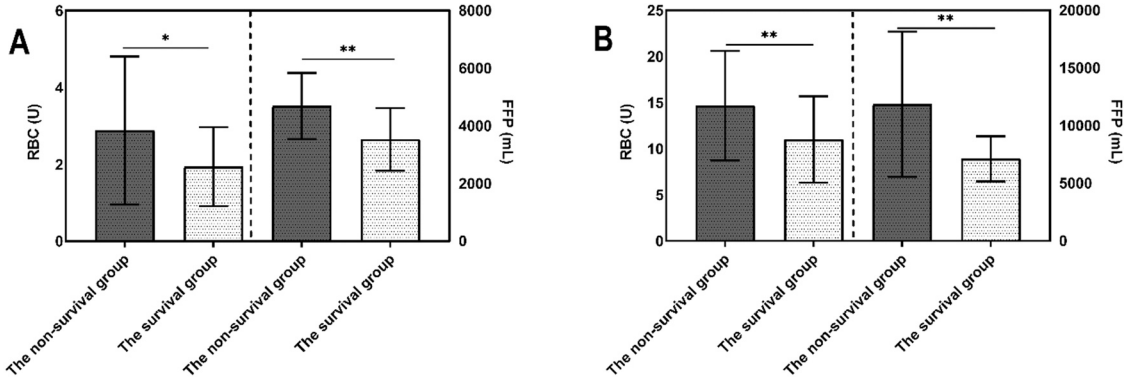

Fig. 3 – Forty-eight hours (A) and total (B) transfusion of FFP and RBC between the survival and non-survival group. The white bars represent the survival group. Black bars represent the non-survival group. Whiskers represent the standard deviation. FFP, fresh frozen plasma; RBC, red blood cells.

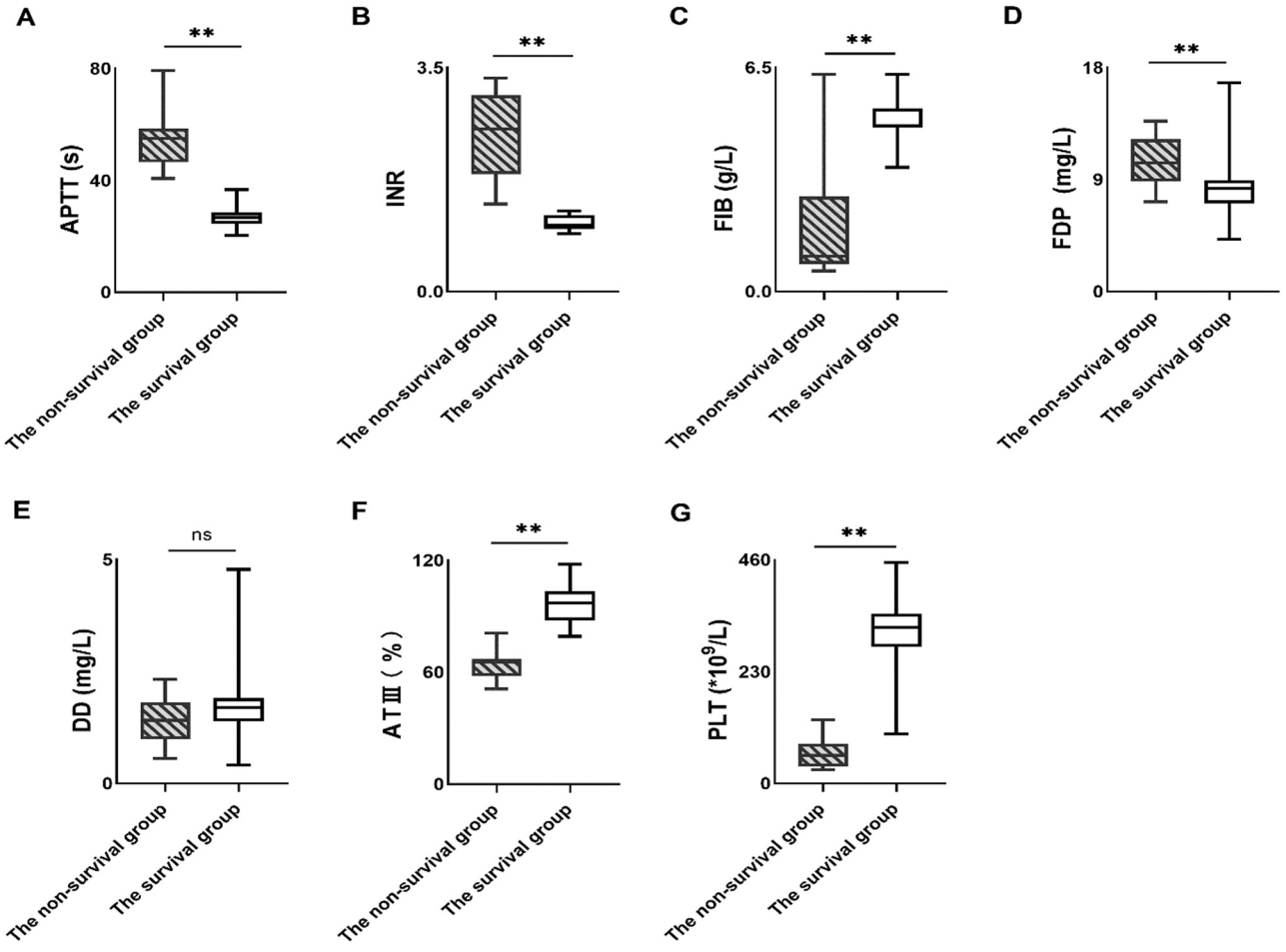

Fig. 4 – Comparison of APTT (A), INR (B), FIB (C), FDP (D), DD (E), ATIII (F), and PLT (G) in the non-survival and the survival groups. Coagulation indexes data are presented as box and whisker plots on the day of death in the non-survival group and 4 weeks post burns in the survival group, with boxes indicating medians and quartiles and whiskers indicating extreme values. Statistical differences were assessed using the Mann-Whitney u-test. ns, non-significant, **, $p < 0.01$.

Table 2 – Clinical data of death cases.

No.	Death time	Sex (F/M)	Age	TBSA (%)	TBSA third degree (%)	ABSI score	Associated injuries	II	Sepsis	Wound culture (time/bacterial species)	Blood culture (time/bacterial species)	PLT (*10^9/L)	INR	APTT (s)	FDP (mg/L)	DD (mg/L)	FIB (g/L)	ATIII (%)	ISTH score
1	2	F	43	90	68	15	TP	Y	N	–	–	132	1.37	40.7	9.83	0.55	5.6	81	1
2	2	M	24	98	72	14	–	Y	Y	2/ S. aureus	–	28	1.75	45.3	12.5	1.09	6.3	65	4
3	3	M	60	63	55	12	MF	Y	Y	3/ P. aeruginosa	3/ P. aeruginosa	78	1.64	53.6	7.9	1.00	3.2	67	4
4	3	M	39	55	34	10	BI	Y	N	–	–	88	2.12	65.2	10.5	2.32	0.6	66	6
5	5	M	56	76	48	13	–	Y	Y	–	–	62	3.16	79.3	8.9	1.90	0.8	78	5
6	8	M	45	44	35	9	–	N	Y	4/ P. aeruginosa 7/ A. baumannii	6/ P. aeruginosa 8/ A. baumannii	81	2.59	56.7	11.3	1.56	1.05	58	5
7	12	M	37	50	36	8	MF	N	N	–	–	53	2.36	47.5	7.2	1.01	0.9	66	6
8	15	M	34	45	40	8	–	N	Y	5/ K. pneumonia 11/ MRSA	7/ K. pneumonia 12/ MRSA	67	3.28	57.6	10.4	0.95	1.35	51	6
9	15	M	33	88	65	13	–	Y	N	6/ S. aureus	9/ S. aureus	49	2.49	46.5	12.7	1.28	1.04	52	5
10	20	M	37	90	76	12	–	N	Y	4/ A. baumannii 12/ S. aureus 19/ MRSE	5/ A. baumannii 12/ S. aureus 20/ MRSE	31	2.59	57.2	8.9	1.56	0.86	59	6
11	25	M	40	64	38	11	–	Y	Y	5/ S. aureus 12/ A. baumannii 17/ MRSA	5/ S. aureus 13/ A. baumannii 19/ MRSA	54	3.34	58.6	13.7	1.89	1.01	67	5
12	27	F	45	40	33	9	CI	N	Y	7/ A. baumannii 11/ P. aeruginosa 18/ K. pneumonia 25/ MRSA	8/ A. baumannii 13/ P. aeruginosa 20/ K. pneumonia 26/ MRSA	29	2.79	49.4	10.3	1.55	0.78	64	6

Abbreviations: F, female; M, male; TBSA, total burned surface area; ABSI, abbreviated burn severity index; TP, tension pneumothorax; II, inhalation injury; MF, multiple fractures; BI, blast injury; CI, craniocerebral injury; N, no; Y, yes; S. aureus, Staphylococcus aureus; A. baumannii, Acinetobacter baumannii; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; MRSA, Multidrug-resistant Staphylococcus aureus; MRSE, methicillin-resistant Staphylococcus epidermidis; ISTH, International Society on Thrombosis and Hemostasis.

post-injury (Fig. 1). The different results may be explained by the fact that the patients included in this study had greater than 30% third-degree TBSA and coagulation testing monitoring lasted for 8 weeks.

Mitra et al. [18] retrospectively discovered hypercoagulability within 24 h of burn injury, while Wiegele et al. [19] reported that patients developed a chromic hypercoagulability two weeks following burn injury using coagulation tests at four-time points. In this study, coagulation dysfunction caused by severe burns was evident as hypercoagulability around one-week post-injury. The primary reason for this could be that the patients received treatment including fluid resuscitation, debridement, and skin grafting within 1 week after injury, resulting in large fluctuations in blood composition, blood remodeling, and hemodilution in a short period. The blood remodeling and hemodilution eventually resulted in a hypercoagulable state. Additionally, a statistical difference in coagulation parameters (APTT, INR, FIB, and PLT) was seen between the non-survival and survival groups following burns (all $p < 0.05$, Fig. 2). On the day of death, nine patients were diagnosed with DIC, and their coagulation parameters were statistically different from those of the survivors (all $p < 0.01$, Table 2 & Fig. 4). These findings may imply that coagulation dysfunction may be a cause of death in patients with severe burns.

We found no statistically significant difference in DD between the 12 dead patients and the survivors, but APTT, INR, and FDP were significantly greater than in the survivor group, and FIB, ATIII, and PLT were significantly lower than in the survivor group (all $p < 0.01$, Fig. 4), implying a hypocoagulable state and hyperfibrinolysis in the coagulation status of the patients who died following severe burns. which suggests that the patients' coagulation cascade is continuously activated after the injury. This finding suggests that the coagulation state plays a role in patient death and may serve as a predictor of patient mortality risk following severe burns. The majority of the patients in this study died two weeks after receiving burns, and they did not have additional opportunities for surgical treatment to heal the burn wound. As a result, these patients had a more difficult time correcting their shocks. It was observed that the number of patients transfused in the non-survival group was significantly higher than the survival group (83.3% vs 40.0%, $p < 0.05$, Table 1), and the volume of infused crystalloids, FFP, and RBC was significantly higher in the non-survival group than in the survival group within 48 hours and throughout the treatment process (all $p < 0.05$, Fig. 3). These findings suggest that excessive fluid resuscitation may be capable of inducing or aggravating coagulation dysfunction in patients with severe burns, and Huzar et al [2,18] also confirmed that fluid resuscitation could affect blood coagulation. Therefore, novel tools, such as thromboelastography [2,20], are required to guide fluid resuscitation, particularly blood product transfusions.

Burn patients who have inhalation injury in addition to sepsis have high mortality [7-10]. In this study, it was observed that the non-survival group had a higher incidence of inhalation injury and sepsis than the survival group (all $p < 0.05$, Table 1). Patients in the non-survival group had significantly greater third-degree TBSA than those in the survival group, which necessitated numerous surgical procedures, lengthening the hospital stay and increasing the risk of infection, and contributing to the high incidence of sepsis. Along with respiratory failure and septic shock, the effects of inhalation injury and sepsis on patients' coagulation are gaining increasing attention [8,10,20]. When the lung epithelium and alveolar macrophages were damaged by inhalation injury, tissue factor was released, activating exogenous coagulation pathways and resulting in pulmonary coagulopathy; hypoxia caused by inhalation injury may result in local thrombosis; sepsis can activate severe burns can activate endogenous coagulation pathways and even result in DIC (Fig. 5). Apart from the increased risk of death, the

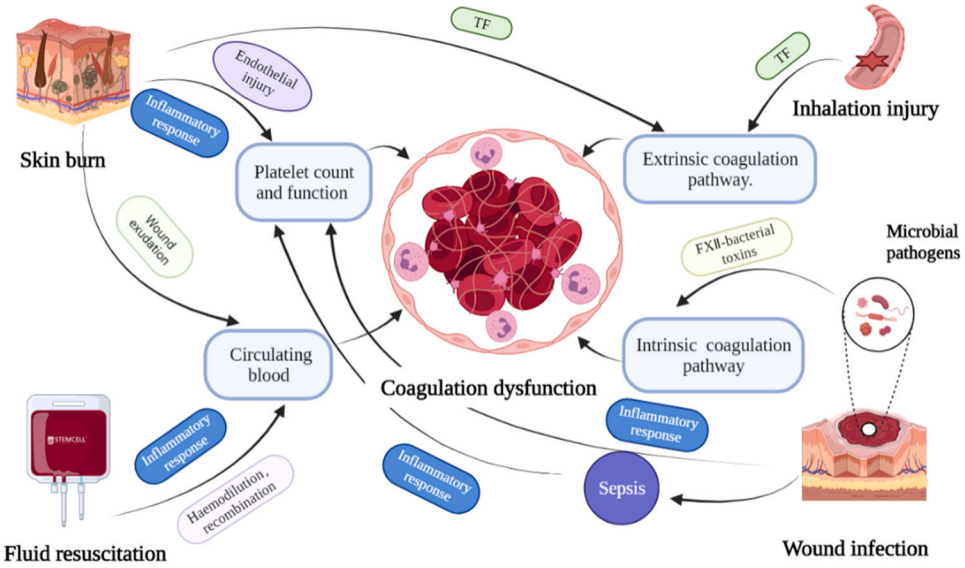

Fig. 5 – Correlation plot between inhalation injury, sepsis, fluid resuscitation, skin burn, and coagulation dysfunction. TF, tissue factor; FXII, coagulation factor XII.

close association between inhalation injury and sepsis with coagulation in patients may exacerbate coagulation dysfunction following severe burns, thus, additional research is needed to elucidate the relationship between inhalation injury, burn sepsis, and coagulation.

Additionally, PLT counts and FIB levels were significantly lower than normal on the day of death in 12 non-surviving patients (Table 2) and also significantly lower than in the surviving group (all $p < 0.01$, Fig. 4). Numerous earlier studies have established that FIB levels and PLT counts are associated with mortality following injury [21-26], however, the current study was unable to reach the same conclusion due to the lack of continuous monitoring of coagulation tests the absence of statistical analysis. In comparison to severe trauma, the situation of blood components loss is more complicated in severe burns [3,15], and wound closure is more challenging. In particular, the non-surviving patients in this study had significantly greater third-degree TBSA than the surviving patients, and the burn wounds took significantly longer to repair and were more frequently infected, during which the endothelium was damaged and the inflammatory response was sustained (Fig. 5). These processes activate PLT and exogenous coagulation pathways, which explains the apparent abnormalities in PLT and FIB.

There are limitations to this study. Firstly, the sample was drawn from a single centre and the size was small. Secondly, the results could have been affected by the treatment and patient population. Additionally, the time points were affected by not having access to the patients' data for the first 7 days, limiting the ability to determine whether hypercoagulability occurred earlier than one week.

5. Conclusions

The coagulation dysfunction of severe burn patients was most prominent at 1 week. Coagulation dysfunction in patients with severe burns can be induced by a large-area burn injury, excessive fluid resuscitation, inhalation injury, and sepsis, which can further develop into DIC and even death. Early blood coagulation testing may be beneficial for diagnosing and monitoring the progression of coagulation dysfunction following severe burns and rational use of blood products may help avoid coagulation dysfunction in these patients.

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Conflict of interest

All authors have no conflict to declare.

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